Full-Length Research Report

# VGF Expression by Monocytes in Patients with Alzheimer's Disease and Vascular Dementia

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**Abstract:** Because its secretion is changed in cerebrospinal fluid and peripheral blood, the neuronal polypeptide VGF (nonacronymic) has been discussed as a biomarker for neuropsychiatric disorders. We have shown an enhanced VGF expression by T-cells from Alzheimer's disease (AD) patients. In this study, we investigated the VGF expression by peripheral monocytes in 38 AD patients, 5 patients with vascular dementia (VD), and 20 neuropsychiatrically healthy individuals using flow cytometry. We determined an enhanced number of VGF-expressing monocytes in VD patients compared to AD patients. VGF+CD14+ monocytes were not correlated with age, body mass index, Mini-Mental State Examination (MMSE), or Q albumin. These preliminary data support findings indicating that VGF might play a role as a peripheral biomarker in VD.

**Keywords:** Alzheimer's disease, vascular dementia, monocytes, VGF, biomarker

## Introduction

Age-related diseases are becoming of great importance, mainly because of increases in population aging and growth (Collaborators, 2019). Between 1990 and 2016, the number of patients with dementia worldwide increased from 20.2 million to 43.8 million. After cardiovascular disorders and cancer, the different forms of dementia are the most frequent diseases in patients over 65 years of age.

60–70% of demented persons suffer from Alzheimer's disease (AD) (Ferri et al., 2005). Clinically, this neurodegenerative disease is characterized by a loss of memory and cognitive functions, while neuropathologically there is a loss of neurons, white matter, and synapses primarily in the hippocampus and the temporal cortex. These neuropathological changes include extracellular amyloid plaques and intracellular neurofibrillary tangles, which might result in neuroinflammation (Calderon-Garciduenas & Duyckaerts, 2017). Microvascular pathologies next to multiple, large volume or lacunar brain infarcts are one of the hallmarks of vascular dementia (VD), the second most common cause of dementia. VD and AD both have several risk factors such as hypertension, diabetes mellitus, and hypercholesterolemia, which are responsible for damage to

the blood-brain barrier. Additionally, microvascular pathologies are observed in AD (Calabro et al., 2021). If this barrier shows dysfunction, the passage of hematopoietic inflammatory cells into the central nervous system (CNS) seems possible.

Microglia are the brain's tissue macrophage and belong to the innate immune cells of the CNS. They account for 10–15% of the adult glial cells in the brain (Nayak et al., 2014). This cell population exhibits an important function since they protect from infections and maintain brain homeostasis (Mandrekar-Colucci & Landreth, 2010). It was shown that microglia take up and dispose of cellular debris, and that they accumulate at the amyloid plaques.

Neuroinflammation is considered to play an important role in AD as well as VD.

Inflammatory processes result in the activation of microglia, which are present in the amyloid plaques (Lue et al., 2010). Cytokines like IL-1beta and IL-6, which initiate similar processes in microglia as well as in the periphery are upregulated in AD compared to nondemented elderly persons (Magalhaes et al., 2018; Ng et al., 2018; Rivera-Escalera et al., 2014).

We determined no age-related alterations in the peripheral frequency of CD14+ monocytes and no differences in

**Table 1.** Demographic data of study cohort

| Characteristics | Controls | AD | p (vs. control) | VD | p (vs. control) | p (vs. AD) |
|---|---|---|---|---|---|---|
| Total (*n*) | 20 | 38 | | 5 | | |
| Age (years; median) | 74.50 | 80.00 | .008 | 80.00 | 0.246 | 1.000 |
| Sex (female/male) | 14/6 | 21/17 | 1.000 | 3/2 | 1.000 | 1.000 |
| BMI (median) | 25.2 | 24.67 | 1.000 | 24.67 | 1.000 | 1.000 |
| MMSE (median) | 29.00 | 18.50 | < .001 | 20.00 | 0.003 | 1.000 |
| p tau (median) | NA | 83.00 | NA | 42.00 | NA | .007 |
| Amyloid-β 1-42 (median) | NA | 444.5 | NA | 501.0 | NA | .248 |
| Amyloid-β ratio (median) | NA | 0.60 | NA | 0.70 | NA | .163 |
| Q albumin (median) | NA | 7.400 | NA | 5.200 | NA | 1.000 |

*Note.* NA = not available.

blood monocytes between AD patients and age-matched neuropsychiatric healthy persons, albeit a decreased number of monocytes in VD patients (Busse et al., 2017; Busse, Steiner, Alter, et al., 2015). We further identified peripheral monocytes that expressed quinolinic acid, a neurotoxic agent (Busse et al., 2018). Therefore, we addressed the question of whether peripheral monocytes express further molecules that might be of particular interest in neurodegenerative disorders.

VFG is such a molecule that might play a role in dementia (Beckmann et al., 2020; Cocco et al., 2010; El Gaamouch et al., 2020; Llano et al., 2019). VGF is widely expressed in the neurons in the brain, especially the hippocampus (Lewis et al., 2015), the brain region that is usually most affected in AD (Jaroudi et al., 2017). VGF plays an important role by improving plasticity, neurogenesis, and energy homeostasis (Behnke et al., 2017; Busse et al., 2012; Sadahiro et al., 2015; Saderi et al., 2014; Thakker-Varia et al., 2014). A disturbance in energy balance is present in diabetes mellitus, which is considered a risk factor for the development of AD (Baglietto-Vargas et al., 2016; Pugazhenthi et al., 2017). Recently, we showed that VGF is expressed by a higher percentage of peripheral CD3+ T-cells from AD patients than in age-matched neuropsychiatric healthy volunteers (Busse, Steiner, Glorius, et al., 2015). In this study, we determined the expression of VGF in monocytes of patients with AD and VD compared with that of nondemented persons.

## Materials and Methods

### Study Cohort

The study was performed in accordance with German regulations, the Declaration of Helsinki, and the guidelines of the local institutional review board. Written consent was obtained from all patients and healthy persons. We collected 18 ml blood from 38 AD patients, 5 VD patients, and 20 sex-matched subjects without neuropsychiatric disorders (the demographic features are summarized in Table 1). A diagnosis of dementia was based on a combination of the patient's history, an examination including neuropsychological testing, and further diagnostics (magnetic resonance imaging and cerebrospinal fluid). A patient's history was characterized by progressive deterioration in cognitive abilities. The Mini-Mental State Examination (MMSE) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) were performed to evaluate the cognitive function of the patients. Patients with AD showed a hippocampal and/or mesiotemporal atrophy and characteristic changes in cerebrospinal fluid (CSF) values (p tau > 50 pg/ml, total tau > 350 pg/ml, Aβ1-42 < 0.8). Routine blood analysis including differential blood cell count, levels of C-reactive protein, glucose, lipids, liver enzymes, and thyroid hormones were also performed. Persons with a history of autoimmune disorders, immunomodulating treatment, cancer, chronic terminal disease, severe cardiovascular disorder, substance abuse, or severe trauma were excluded from the study.

### Preparation of Peripheral Blood Monocyte Cells (PBMC)

Peripheral blood mononuclear cells (PBMCs) were separated by standard density gradient centrifugation (Ficoll Paque; Biochrom AG, Berlin) for 20 min, 375x g, at room temperature, from freshly drawn blood collected in lithium heparin-treated tubes (BD Vacutainer; BD Biosciences, San Jose, CA, USA), which was diluted 1:1 with phosphate-buffered saline (PBS). The cell ring between Ficoll Paque and PBS was harvested, and the cell suspension was centrifuged and washed twice in PBS. Cells were suspended in staining buffer (PBS w/0.5% BSA), and the cell number was determined.
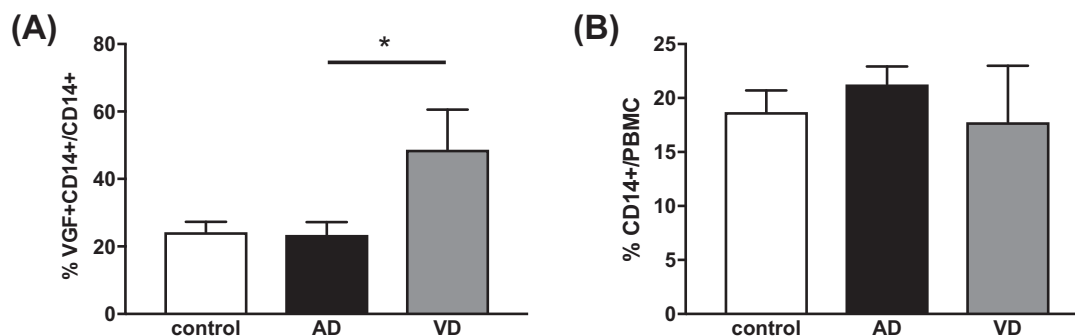
**Figure 1.** VGF+CD14+ monocytes are increased in VD patients. The number of VGF-expressing monocytes (A) and the number of monocytes (B) were determined in peripheral blood of 38 AD and 5 VD patients and 20 neuropsychiatric healthy control persons. *$p < .05$.

## Flow Cytometry

Isolated PBMCs were washed once and then incubated with fluoresce-labeled antibodies for 20 min at 4 °C in staining buffer (1% BSA in PBS). Antibodies (Abs) used in this study included reagents specific for CD14 (TÜK4) from Miltenyi Biotec (Bergisch Gladbach, Germany); VGF (D-20) and the detection antibody, donkey anti-goat IgG FITC, from Santa Cruz (Dallas, TX, USA). Data were collected on LSR-Fortessa and analyzed using FACS DIVA software (BD Biosciences, Mountain View, CA, USA). The frequency of cells was shown by using the biexponential transformation function for complete data visualization.

## Statistical Analysis

Statistics were performed using SPSS 26 and GraphPad Prism 7. Shapiro-Wilk tests were performed to test for normal distribution. In dependence of the obtained results, the differences between the groups were calculated by one-way ANOVA or Kruskal-Wallis H-test, followed by Bonferroni posthoc tests. Gender differences were calculated using the chi-square test. Correlation analyses were performed using Spearman analysis. Significance was defined as $p < .05$.

## Results

### The Expression of VGF in Monocytes Is Enhanced in VD Patients

In the elderly neuropsychiatrically healthy control group, the median frequency of CD14+ monocytes in the PBMC fraction was 18.5% (Table 1). This number decreased in VD patients to 13.2%, whereas in AD patients it was nearly unchanged (19.3%).

In the group of neuropsychiatrically healthy persons, on average 21.3% of monocytes expressed VGF. At the time

when AD was diagnosed, the percentage of monocytes expressing VGF was 15%, the frequency of VGF+CD14+ cells from VD patients enhanced to 36.5% ($p = .034$; see Figure 1).

## Correlation of VGF Expression by Monocytes with Age and Q albumin

Since we determined an age-dependent increase in the frequency of VGF-expressing T-cells in healthy individuals (Busse et al., 2014) and with enhancing BMI values (Busse et al., 2014), we addressed the question of whether age, BMI, MMSE, and Q albumin also influenced the expression of VGF by CD14+ monocytes.

First, because of age differences between the control group and the demented groups, we found that age negatively influenced the MMSE values. Moreover, age also influenced Q albumin as well as the Aβ ratio, especially in AD, especially in female patients (Table 2).

However, no significant correlations were determined between age (Figure 2A), BMI (Figure 2B), MMSE (Figure 2C), or Q albumin (Figure 2D) and the frequency of VGF-expressing CD14+ monocytes, neither in the total study cohort (Figure 2) nor in the individual control, AD, and VD groups (data not shown).

## Discussion

The present study found that monocytes obtained by VD patients expressed more VGF than monocytes from AD patients or elderly neuropsychiatric healthy persons, while the frequency of peripheral CD14+ monocytes was not changed.

Our results are in line with our previous finding showing no differences in the percentage of CD14+ cells from AD patients at the time of diagnosis compared to the control group (Busse, Steiner, Alter, et al., 2015), while in VD

**Table 2.** Influence of age

| Variable | Total age | Group | | | Gender | |
|---|---|---|---|---|---|---|
| | | Age controls | Age AD | Age VD | Female | Male |
| BMI | | | | | | |
| Rho | −0.375 | −1.000 | −0.239 | −1.000 | −0.266 | −0.490 |
| p | 0.034* | | 0.230 | < 0.001*** | 0.302 | 0.064 |
| MMSE | | | | | | |
| Rho | −0.310 | 0.075 | 0.001 | −0.400 | −0.276 | 0.011 |
| p | 0.024* | 0.807 | 0.997 | 0.600 | 0.133 | 0.966 |
| Amyloid-beta 1-42 | | | | | | |
| Rho | −0.027 | NA | −0.039 | −0.100 | −0.024 | 0.011 |
| p | 0.867 | | 0.821 | 0.873 | 0.916 | 0.966 |
| Phospho tau | | | | | | |
| Rho | 0.036 | NA | 0.106 | −0.500 | 0.196 | −0.062 |
| p | 0.819 | | 0.533 | 0.391 | 0.370 | 0.800 |
| Amyloid-beta ratio | | | | | | |
| Rho | −0.370 | NA | −0.488 | 0.462 | −0.575 | −0.013 |
| p | 0.016* | | 0.002** | 0.434 | 0.004** | 0.957 |
| %VGF+CD14+/+CD14+ | | | | | | |
| Rho | −0.008 | 0.136 | −0.026 | 0.800 | −0.028 | 0.068 |
| p | 0.949 | 0.567 | 0.878 | 0.104 | 0.868 | 0.742 |
| %CD14+ | | | | | | |
| Rho | 0.014 | −0.003 | −0.181 | −0.200 | 0.122 | −0.024 |
| p | 0.916 | 0.990 | 0.278 | 0.747 | 0.472 | 0.906 |

*Note.* $*p < .05$, $**p < .05$, $***p < .005$.
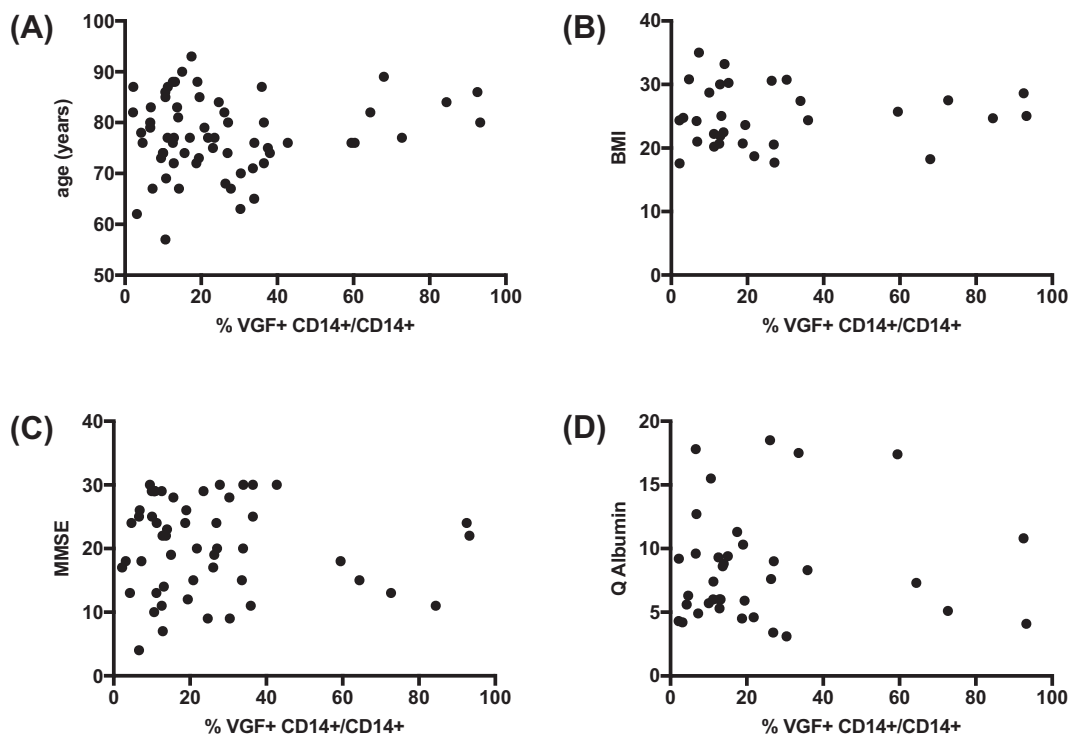


**Figure 2.** Correlations between age, BMI, MMSE, and Q albumin and the frequency of VGF-expressing CD14+ monocytes. No significant correlations were determined between age (A), BMI (B), MMSE (C), and Q albumin (D) and the frequency of VGF-expressing CD14+ monocytes in the total study cohort.

patients the number of CD14+ monocytes was decreased (Busse et al., 2017).

Although changes in blood cell profile of the AD and VD types of dementia are not yet fully understood, some reports show an altered peripheral blood cells profile. Chen et al. (2017) discovered a decreased population of lymphocytes and basophils in AD patients compared with controls, but an unaltered level of monocytes. In contrast, Lunnon et al. (2012) revealed an increase in the number of monocytes in the blood of patients with AD. In this study, we show that VGF is expressed by a higher percentage of peripheral CD14+ monocytes from VD patients than in age-matched neuropsychiatric healthy volunteers and in AD patients.

VD is characterized by strokes and vascular damage. This also often means a lack of the blood-brain barrier (BBB) (Ueno et al., 2016). As a result of the disturbed BBB, monocytes can immigrate into the brain. In their review, Han et al. (2020) described that, following an acute ischemic stroke, peripheral monocytes infiltrate into the lesion site within 24h and peak at 3 to 7 days. Increasing evidence indicates that alterations of the cerebral microcirculation may also play a role in AD (Park et al., 2017). Because a dysfunctional BBB is also often associated with AD, there are great similarities between AD and VD (Burgmans et al., 2013). In contrast to patients with VD, however, we did not find any increased expression of VGF in monocytes in patients with AD. A decisive neuropathological difference between AD and VD lies in the amyloid plaques surrounded by activated microglia.

We previously showed that the expression of VGF by peripheral T-cells is age-dependent (Busse et al., 2014). In our present study, however, we did not detect a correlation between age and VGF-expressing monocytes, although the control persons were younger than the demented patients. Since we did not include healthy persons from younger age brackets, we cannot draw any conclusion whether the VGF expression by monocytes changes with enhanced age in healthy persons.

Recently, it was shown that the expression of VGF is required by rapid-acting antidepressants that modulate N-methyl-D-aspartate receptor (NMDA-R) signaling (Jiang et al., 2019). This is of particular interest since the NMDA-R is very important in the pathology of AD (Foster et al., 2017). In this context, it is interesting to note that serum VGF levels were significantly lower in patients with major depressive disorder than in bipolar depression (BD) patients, but higher in BD patients compared to healthy control individuals. No correlation was found between serum VGF levels and any data of persons (Chen et al., 2019).

The frequency of VGF-expressing T-cells increased with enhanced BMI (Busse et al., 2014). On the other hand, the VGF peptides NAPPE and TLQP were significantly reduced in the plasma of obese persons, defined by BMI (D'Amato et al., 2015). The frequency of VGF-expressing CD14+ monocytes was not altered by BMI.

It was shown that VGF levels in CSF were lower in Lewy body dementia (LBD) than in AD patients or controls and are associated with a stronger cognitive decline. VGF in LBD was positively correlated with tau, but not Aβ1-42 in CSF (Van Steenoven et al., 2019). Another group found a decreased VGF level in CSF of AD patients (Sathe et al., 2019). However, the frequency of VGF+ monocytes was not correlated with the mental state of the study cohort nor with the cognitive decline in AD and VD patients. It remains to be clarified whether the plasma or serum level of VGF is altered in AD and VD as well, and whether there is a correlation between CSF and plasma/serum VGF level.

The present study has a certain limitation that must be considered: We analyzed the VGF expression in 38 AD patients, but only in 5 patients with VD. Further studies should confirm these preliminary data.

Taken together, VGF is expressed by monocytes, but while the expression level is not altered between AD patients and nondemented controls, it is increased in VD. Since it is not correlated with age, BMI, MMSE, or Q albumin, it might be rather associated with a VD-specific characteristic.

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